PATENT SPECIFICATION

NO DRAWINGS

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1,134,687

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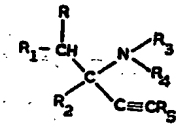
COMPLETE SPECIFICATION

Acetylenic Compounds

We, BEECHAM GROUP LIMITED, a British Company of Beecham House, Great West Road, Brentford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a modification of the invention described in British Patent Specification 1,041,987 by providing a new process for preparing certain of the acetylenic amines described therein, further examples of those amines, and also some new compounds of closely related structure.

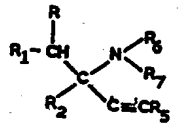
The compounds described and claimed in British Patent Specification No. 1,041,987 are of general formula (I)



(I)

and non-toxic acid addition and quaternary ammonium salts thereof, wherein R is a hydrogen atom or an alkyl group containing 1—3 carbon atoms; R_1 is a hydroxy, alkoxy, acyloxy, carbamoyloxy, aryloxy or aralkoxy group or a halogen atom; R_2 is an alkyl, aryl or aralkyl group; and R_3 and R_4 are the same or different and each is a hydrogen atom or an alkyl, alkynyl, hydroxyalkyl or aralkyl group, or R_3 and R_4, together with the N atom to which they are attached, form a 5- or 6-membered heterocyclic ring system; and R_5 is a hydrogen atom, an alkyl or aryl group or a cyclopentyl or cyclohexyl group.

It has now been found that additional novel compounds with pharmacological activity, including activity as hypotensives, are those in which R_3 and/or R_4 are aminoalkyl groups, and so this invention provides compounds of formula (II)

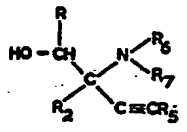


(II)

and non-toxic acid addition and quaternary ammonium salts thereof, wherein R, R_1, R_2 and R_5 are as defined above and R_6 and R_7 are the same or different and each is a hydrogen atom or an alkyl, alkynyl, hydroxyalkyl, aminoalkyl or aralkyl group or R_6 and R_7, together with the N atom to which they are attached, form a 5- or 6-membered heterocyclic ring system: most of these compounds are already covered by formula (I) and so this invention provides as new compounds those compounds of formula (II) which are not included within the definition of formula (I), and also further examples of formula (I) not specifically described before.

Since the compounds of the present invention contain asymmetric centres, they can exist in several optically active forms, and the present invention extends to these optically active forms as well as to the corresponding racemic mixtures.

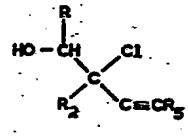
When R_1 is a hydroxy group in formula (II) the compounds are of formula (III)



(III)

and non-toxic acid addition and quaternary ammonium salts thereof.

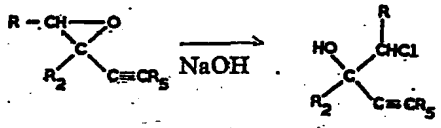
This invention also provides a new process for preparing the compounds of formula (III) wherein a chlorocarbinol of formula (IV)



(IV)

(or a derivative thereof in which the hydroxy group has been protected by reaction with a vinyl ether such as ethyl vinyl ether or preferably with 2,3-dihydropyran) is reacted with ammonia or an amine of the formula R_6R_7NH (and subsequently, if necessary, removing the protecting group by acid hydrolysis). The reaction of the chlorocarbinol is preferably with an excess of the primary or secondary amine HNR_6R_7 at or below room temperature (which is hereby defined as 25°C) in presence of a catalytic quantity of copper bronze. The decision as to whether a protecting group for the hydroxy group is needed depends on i) the other substituents present because some of the chlorocarbinols of formula (IV) are unstable (for example 3 - chloro - 4 - hydroxy - 3 - phenylbut-1 - yne) and (ii) also on the other reactant and the reaction conditions: for example if HNR_6R_7 is to be ammonia the chlorocarbinol (IV) is usually protected and the amination is preferably carried out using liquid ammonia in the presence of sodamine, or if HNR_6R_7 is to be an alkylenediamine, the chlorocarbinol (IV) is usually protected and the reaction preferably carried out using an alkali metal derivative of the amine. After this reaction preparing the compounds of formula (III), the hydroxy group may be esterified, etherified or halogenated to give further compounds of formula (II). Also when R_6 and/or R_7 are hydrogen atoms the compounds of formula (II) or (III) may be alkylated, alkynylated, hydroxy-alkylated or aralkylated to give further compounds of formula (II), and when R_6 is a t-butyl group the compound may be pyrolysed to give a compound in which R_6 is a hydrogen atom. These types of subsequent reactions are described and exemplified in more detail in British Patent Specification No. 1,041,987. Furthermore any of the basic amine compounds of the formula (II) or (III) can also be converted to their acid addition salts or quaternary ammonium salts in conventional manner or likewise acid addition salts can be converted to the free base forms in conventional manner. These subsequent reactions are also described and exemplified in more detail in British Patent Specification No. 1,041,987.

The starting chlorocarbinols of formula (IV) are conveniently prepared from isomeric chlorocarbinols of formula (V) by treatment with an alkali metal hydroxide in an ether solvent to form an epoxide of formula (VI),



(V) (VI)

and treating this with hydrogen chloride in ether or with concentrated hydrochloric acid. This treatment of the epoxide (VI) often gives mixtures of the desired chlorocarbinol of formula (IV) and the starting isomeric chlorocarbinol of formula (V), and the conditions must be chosen for optimum yields of the desired isomer (IV); for example 10 N hydrochloric acid containing calcium chloride is used in some instances.

The chlorocarbinol of formula (V) and the epoxide of formula (VI) above are the starting materials used in the process described in British Patent Specification No. 1,041,987, which describes their direct conversion to the compounds of formula (I).

The compounds of formula (II) may be employed as pharmacological agents in admixture with other active ingredients and/or suitable pharmaceutical carriers. These pharmaceutical carriers may be any ingredients which are used in the manufacture of specific formulations for oral, parenteral, topical or rectal use, such as solvents, bulking agents, surface active agents, colouring agents, lubricants, coating materials, flavours, et cetera. Thus, in another aspect this invention provides pharmaceutical formulations containing a compound of formula (II) other than those containing a compound of formula (I) which are already claimed in British Patent Specification No. 1,041,987.

Having now described the invention, the following examples illustrate it in several aspects, though these examples should not be regarded as limiting the scope in any way.

EXAMPLE 1

3 - Chloro - 3 - hydroxymethylbut - 1-yne (1.18 g.), n-butylamine (3.65 g., 4.95 ml.) and water (0.36 ml.) were mixed and cooled to 5°C. Copper bronze (0.01 g.) was added and the reaction mixture was stirred for 1¾ hours with warming to room temperature. The mixture was diluted with water, acidified with 10 N hydrochloric acid, and any neutral materials were extracted into ether. Basification of the aqueous phase with 40% sodium hydroxide solution was followed by extraction with ether, drying of the ether extracts and removal of solvent *in vacuo* to give an oil (1.23 g.) which solidified to a waxy solid. Conversion of this material to its hydrochloride with ethereal hydrogen chloride, followed by crystallisation from methanol/acetone gave 3 - n - butylamino-3 - hydroxymethylbut - 1 - yne hydrochloride (0.60 g., 31%) m.p. 142—144°C.

The starting chloro compound was prepared as follows. 3,4 - Epoxy - 3 - methylbut - 1 - yne was prepared from 3 - chloromethylbut - 1 - yn - 3 - ol (59.25 g.) by stirring for 18 hours in ether (500 ml.) with 40% sodium hydroxide solution (250 ml.). Without isolation, the epoxide in ether was added to a stirred solution of calcium chloride (112 gm.) in 10 N hydrochloric acid (400 ml.) cooled in an ice bath. After stirring vigorously for 1 hour, the mixture was diluted with water (500 ml.), and the aqueous layer separated and washed with ether (3×100 ml.). The combined ether solutions were washed with saturated sodium bicarbonate solution to pH 8 and dried ($MgSO_4$). Removal of solvent *in vacuo* gave an oil (46.6 g.), which was distilled to give 3 - chloro - 3 - hydroxymethylbut - 1 - yne (36.9 g., 62%, purity 92%), b.p. 47°C/10—12 mm., n_D^{21} 1.4683. This material was stabilised by storage over magnesium oxide.

EXAMPLE 2

3 - Methylamino - 3 - hydroxymethylbut-1 - yne was prepared as described in Example 1, and isolated as the *hydrochloride* (60%) m.p. 148—149°C ex. methanol/acetone (Found: C, 48.3; H, 8.0; Cl, 24.0; N, 9.2%. $C_6H_{12}ClNO$ requires: C, 48.2; H, 8.1; Cl, 23.7; N, 9.3%). From this hydrochloride was liberated the free *base*, m.p. 43—44°C. (Found: C, 63.4; H, 9.8; N, 12.0%; $C_6H_{11}NO$ requires: C, 63.7; H, 9.8; N, 12.4%).

EXAMPLE 3

Sodamide was prepared in liquid ammonia (70 ml.) from sodium (1.52 g.) in the presence of a trace of ferric nitrate. To this mixture cooled to —60°C was added 3-chloro - 3 - (2' - tetrahydropyranyloxymethyl)but - 1 - yne (12.15 g.) in dry ether (50 ml.) over 20 minutes. After stirring for 1½ hours, the ammonia was allowed to evaporate overnight. Ether was removed *in vacuo* and the residue decomposed by the addition of crushed ice. After acidification with 10 N. hydrochloric acid, the upper oily layer was extracted into ether, and the residual aqueous layer heated at 60°C for 2 hours to complete the removal of the protecting group. After basification with 40% sodium hydroxide solution and saturation with salt, the aqueous solution was continuously extracted with ether for 2½ hours. After drying the ether extract ($MgSO_4$) and evaporation of solvent there remained an oil (6.06 g.) which was distilled, b.p. 76—86°C/9 mm. Treatment of the distillate (2.93 g.) with ethereal hydrogen chloride gave 3 - amino-3 - hydroxymethylbut - 1 - yne hydrochloride (4.09 g., 50%) m.p. 146—147°C, which crystallised from methanol/acetone as colourless plates m.p. 148—149°C.

3 - Chloro - 3 - (2' - tetrahydropyranyloxymethyl)but - 1 - yne (77%), b.p. 100—105°C/10 mm., $n_D^{19.5}$ 1.4703, was prepared from 3 - chloro - 3 - hydroxymethylbut-1 - yne and a 10% excess of 2,3-dihydrogen in the presence of a trace of ethereal hydrogen chloride.

EXAMPLE 4

3 - Chloro - 3 - phenyl - 4 - (2' - tetrahydropyranyloxy)but - 1 - yne (5.29 g.), n-propylamine (8.2 ml.) and water (0.36 ml.) were mixed and cooled to —20°C. Copper bronze (0.05 g.) was added, and the mixture was stirred for 30 minutes at —20°C followed by 5 hours at room temperature. Water (10 ml.) and 10 N hydrochloric acid (12 ml.) were then added, and the reaction mixture stirred for 30 minutes in order to remove the protecting group. After decanting from some tarry material, the solution was extracted with ether to remove neutral materials, basified with 40% sodium hydroxide solution, and the liberated oil was extracted into ether (5×50 ml.). Removal of solvent after drying ($MgSO_4$) gave an oil (5.16 g.) which was distilled, b.p. 96—110°C/0.1 mm. The distillate (1.81 g.) solidified to a waxy solid, which was crystallised from light petroleum (b.p. 40—60°C) to give 4 - hydroxy - 3-phenyl - 3 - n - propylaminobut - 1 - yne (1.05 g., 26%) m.p. 53—54°C. A similar experiment carried out on the unprotected 3 - chloro - 4 - hydroxy - 3 - phenylbut-1 - yne gave the same material in lower yield (11%).

The starting chloro compound was prepared as follows. 3,4 - Epoxy - 3 - phenylbut - 1 - yne (2.9 g.) prepared from 4-chloro - 3 - phenylbut - 1 - yn - 3 - ol and powdered sodium hydroxide in ether, was dissolved in dry ether (50 ml.), cooled to —60°C and stirred during the addition of excess ethereal hydrogen chloride (20 ml.). Stirring was continued at —60°C for 10 minutes and then until the solution had

warmed to −10°C. Excess acid was neutralised by washing with sodium bicarbonate solution, and the ether solution dried ($MgSO_4$). Removal of solvent *in vacuo* in the cold left 3 - chloro - 4 - hydroxy - 3-phenylbut - 1 - yne as a yellow oil (3.6 g.), which rapidly darkened and slowly evolved hydrogen chloride. It could be used immediately or stored in ether solution over magnesium oxide.

Reaction of the above compound with a 10% excess of 2,3 - dihydropyran in the presence of a catalytic quantity of ethereal hydrogen chloride gave the protected derivative, 3 - chloro - 3 - phenyl - 4 - (2′ - tetrahydropyranyloxy)but - 1 - yne.

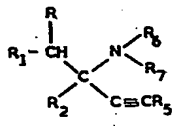
EXAMPLE 5

To sodium hydride (2.04 g.) in dry tetrahydrofuran (30 ml.) was added anhydrous ethylenediamine (50 ml.) at 0°C. over 15 min. During the addition, a slow evolution of hydrogen took place which became rapid on warming to 40°C. When evolution of gas was complete, the mixture was cooled to 0°C. and 3 - chloro - 3 - (2′ - tetrahydropyranyloxymethyl)but - 1 - yne (14.49 g.) in tetrahydrofuran (20 ml.) added dropwise over 15 min. After stirring overnight, the solid which had formed was filtered off, and the filtrate evaporated *in vacuo*. The residue was dissolved in water (25 ml.) and conc. hydrochloric acid (17 ml.), and stirred for 2½ hr. to remove the protecting group. After extraction with ether, the aqueous solution was basified, and continuously extracted for 9 hr. to give an oil (7.53 g.) which was converted to a gummy hydrochloride. Crystallisation of this material from methanol-acetone, afforded 3 - (β - aminoethyl)amino-3 - hydroxymethylbut - 1 - yne hydrochloride (7.6 g., 50%) m.p. 207.5—208.5°C (decomp.). The melting point was raised to 208—209°C on recrystallisation from the same solvent mixture (Found: C, 39.3; H, 7.8; Cl^- 33.55; N, 13.1%. $C_7H_{16}Cl_2N_2O$ requires: C, 39.1; H, 7.4; Cl^- 33.0; N, 13.0%). From this hydrochloride was liberated the free *base*, m.p. 83.5—85°C. (Found: C, 58.9; H, 10.1; N, 20.0%. $C_7H_{14}N_2O$ requires: C, 59.2; H, 9.9; N, 19.7%).

A similar experiment carried out using an equivalent quantity of sodium amide instead of sodium hydride, gave the same product in 32% yield.

WHAT WE CLAIM IS:

1. A compound of formula (II)



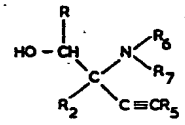
(II)

and non-toxic acid addition and quaternary ammonium salts thereof, wherein R is a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms, R_1 is a hydroxy, alkoxy, acyloxy, carbamoyloxy, aryloxy aralkoxy group or a halogen atom, R_2 is an alkyl, aryl or aralkyl group R_6 and R_7 are the same or different and each is a hydrogen atom or an alkyl, alkynyl, hydroxyalkyl, aminoalkyl or aralkyl group or R_6 and R_7, together with the N atom to which they are attached, form a 5 or 6 membered heterocyclic ring system, and R_5 is a hydrogen atom or an alkyl, aryl, cyclopentyl or cyclohexyl group, other than those compounds which are also covered by formula (I) is set out before in this specification and which are claimed in claim 1 of British Patent Specification No. 1,041,987.

2. 3 - Methylamino - 3 - hydroxymethylbut - 1 - yne and non-toxic acid addition salts thereof.

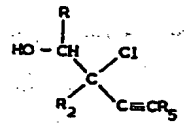
3. 3 - (β - Aminoethyl)amino - 3-hydroxymethylbut - 1 - yne and non-toxic acid addition salts thereof.

4. A process for preparing compounds of formula (III)



(III)

(in which R, R_2, R_5, R_6 and R_7 are as defined in claim 1) wherein a chlorocarbinol of formula (IV)



(IV)

(or a derivative thereof in which the hydroxy group has been protected by reaction with a vinyl ether) is reacted with ammonia or an amine of the formula R_6R_7NH (and subsequently, if necessary, the protecting group is removed by acid hydrolysis).

5. A method as claimed in claim 4 wherein the hydroxy group in the compound of formula (III) is protected by reaction with 2,3-dihydropyran and the tetrahydropyran-2-yl protecting group is subsequently removed by acid hydrolysis.

6. A method as claimed in claim 4 or 5 wherein the reaction is carried out at or below room temperature (which is hereby defined as 25°C) using an excess of the primary or secondary amine of formula

R_6R_7NH in the presence of a catalytic quantity of copper bronze.

7. A process as claimed in claim 4 or 5 wherein the compound of formula (IV) has its hydroxy group protected, the compound of formula R_6R_7NH is ammonia, and the reaction is carried out in liquid ammonia in the presence of sodamide.

8. A process as claimed 4 or 5 wherein the compound of formula (IV) has its hydroxy group protected and the compound of formula R_6R_7NH is an alkylenediamine which is used in the form of an alkali metal derivative.

9. A process for preparing an acetylenic amine of formula (III) substantially as described with reference to any one of Examples 1 to 5 hereinbefore set forth.

10. Acetylenic amines of formula (III) when prepared by a process as claimed in any one of claims 4 to 8.

11. A pharmaceutical composition comprising a pharmaceutical carrier and an acetylenic amine of formula (II) as claimed in claim 1.

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